

(12)

EUROPEAN PATENT SPECIFICATION

- (45) Date of publication of patent specification: **08.02.84** (51) Int. Cl.³: **A 61 K 7/48**
(21) Application number: **80200929.0**
(22) Date of filing: **02.10.80**

(54) **Anti-acne composition comprising diisopropyl sebacate.**

(30) Priority: **12.10.79 US 84252**

(43) Date of publication of application:
22.04.81 Bulletin 81/16

(45) Publication of the grant of the patent:
08.02.84 Bulletin 84/6

(84) Designated Contracting States:
BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP - A - 0 001 871
FR - A - 2 368 949
GB - A - 1 048 820
GB - A - 1 152 644
US - A - 4 052 513

**H. JANISTYN: "Handbuch der Kosmetika und
Riechstoffe", vol. 1, 3rd edition, 1978, page 177
Heidelberg. DE. A. Hüthig: "Die kosmetischen
Grundstoffe"**

**The file contains technical information
submitted after the application was filed and not
included in this specification**

(73) Proprietor: **THE PROCTER & GAMBLE COMPANY**
301 East Sixth Street
Cincinnati Ohio 45202 (US)

(72) Inventor: **Luedders, Wilmer Louis**
1983 Connecticut Avenue
Cincinnati Ohio (US)

(74) Representative: **Suslic, Lydia et al,**
Procter & Gamble European Technical Center
Temselaan 100
B-1820 Strombeek-Bever (BE)

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European patent convention).

Anti-acne composition comprising diisopropyl sebacate

Acne vulgaris and other types of acne and acneiform skin maladies associated with the hyperplasia of the sebaceous follicle are often treated by the oral administration of antibiotics. Tetracycline has been the traditional drug of choice, but other antibiotics such as erythromycin, lincomycin and clindamycin have also been prescribed for this use. While oral administration of these
 5 drugs is often effective in treating acne, oral therapy has several disadvantages. For example, the oral administration of antibiotics subjects the entire body to the antibiotic composition; yet, in acne, only the skin is affected. Moreover, almost all antibiotics have some undesirable side effects when taken orally.

In contrast with oral dosing in the treatment of acne, topical application of antibiotics delivers the antibiotic to the afflicted situs and minimizes the antibiotic levels in the circulatory and gastrointestinal
 10 systems. Undesirable side effects occurring from oral administration of the drug are greatly reduced, and yet, properly administered in the manner disclosed herein, the therapeutic benefits of topical application are comparable with, or superior to, those derived by oral administration.

A problem with this approach is that the effectiveness of any particular antibiotic as a topical treatment of acneiform skin diseases depends significantly upon the particular skin penetrating vehicle
 15 with which it is used.

One agent, isopropyl myristate, has been used with some success in enhancing the percutaneous penetration of erythromycin. However, isopropyl myristate has the undesirable characteristic of promoting the formation of comedones, or blackheads. Thus, it would be desirable to develop new, more dermatologically acceptable penetration enhancers for erythromycin.

Unfortunately, the field of percutaneous absorption remains highly empirical. A leader in this field, Dr. Richard B. Stoughton, has aptly summarized the problem: There are two rather distinct groups of researchers in the field of percutaneous absorption. They are probably best classified as the theoreticians and the practitioners.

The theoreticians are primarily physical chemists who establish strict mathematical relationships
 25 of penetration based on general theory and observations of simple membrane structures. In general, they try to avoid working with human or animal skin because these perverse models generally fail to substantiate their predictions based on simpler systems and theoretical models.

The practitioners have to admit to their studies being more an art than a science but they have the responsibility (and the great advantage) of working with a live, functioning model. Without detailed
 30 knowledge of higher mathematics or physical chemistry, these practitioners are best described as belonging to the "apply and observe" school. (Dr. R. B. Stoughton, *J. Invest. Derm.*, 63 (4):305—305 (1974)).

This invention relates to erythromycin-containing compositions which have been empirically determined to cause erythromycin to penetrate skin when applied topically.

French 2,383,667, S. Desjonqueres, published on 10 October, 1978, describes topical erythromycin compositions in which rapid penetration of the antibiotic into the sebaceous follicles is achieved. The excipient bases include alkyl esters of fatty acids such as lauric, linoleic, myristic and oleic acids.

Compositions for topical treatment of acne are known. Smith, U.S. 3,952,099, issued April 20,
 40 1976, discloses compositions for treating acne lesions by topical application of tetracycline antibiotics in a skin penetration vehicle comprising sucrose monooleate, decyl methyl sulfoxide and alcohol.

Stoughton, U.S. 3,969,516, issued July 13, 1976, and *Arch. Dermatol.*, 84 182 (1976), discloses a method for topically treating acne by applying formulations containing various antibiotics in N-methyl-2-pyrrolidone. The data presented are said to indicate that tetracycline in a pyrrolidone-based
 45 penetrating vehicle does not effectively control the inflammatory lesion of acne. In addition to tetracycline, compositions of erythromycin, erythromycin derivatives and clindamycin in the same vehicle were studied. The combination of erythromycin and N-methyl-2-pyrrolidone gave results which were assertedly better than tetracycline in the same vehicle, whereas the antibiotic lincomycin gave superior results in controlling the inflamed lesions.

French 2,368,949, The Procter and Gamble Company, published 26 May, 1978, describes formulations containing erythromycin, useful in the topical treatment of acne. The vehicles used in these compositions include mixtures of ethanol and isopropyl myristate; diisopropyl sebacate is not disclosed.

European Patent Application A—1871, The Procter & Gamble Company, filed 8 November,
 55 1978, published 16 May, 1979, discloses zinc erythromycin compositions which are useful in the topical treatment of acne.

This invention relates to antibiotic compositions especially adapted for the treatment of skin disorders and dermatoses of bacterial origin, including *Acne vulgaris* and other acneiform skin diseases (hereafter "acne"). The compositions herein comprise a safe and effective amount of erythromycin
 60 and/or compounds of erythromycin and a pharmaceutically acceptable penetrating carrier.

By "afflicted situs" is meant the areas of the skin which is inflamed, the acne comedones, papules, pustules, and cysts (acne lesions) and the skin immediately surrounding this area.

By "antibiotic agent" is meant erythromycin base and derivatives of erythromycin. These antibiotic agents can be used alone or in combination in the present compositions.

By "pharmaceutically acceptable" and "dermatologically acceptable" is meant that the ingredients are suitable for use in contact with the skin and tissues of humans and lower animals without any untoward physiological response, commensurate with a reasonable benefit/risk ratio.

By "safe and effective amount" is meant an amount which is effective to alleviate the inflammation and the lesions of the dermatological condition and yet cause no undesirable side effects (at a reasonable benefit/risk ratio). For topical application, a dose range of antibiotic composition of from about 0.1 mg/cm² per day to about 25 mg/cm² per day is effective. The dosage can vary from patient to patient, depending on such factors as the severity of the disease, the frequency of application, the area of the body which is afflicted, and the particular erythromycin compound being applied.

By "topical application" is meant directly spreading or laying on epidermal tissue. The application can be made by rubbing, by using medicated pads, or by any other convenient means.

By "erythromycin" is meant erythromycin base produced by the strain of *Streptomyces erythreus*. The term includes both erythromycin base and/or its hydrated crystals. By the term "derivatives of erythromycin" is meant the salts between erythromycin base and acids, as well as the ester derivatives of erythromycin. Non-limiting examples of derivatives of erythromycin include: erythromycin estolate, which is the lauryl sulfate salt of the propionic acid ester of erythromycin; erythromycin glucoheptonate, which is the glucoheptonic acid salt of erythromycin; erythromycin lactobionate, which is prepared from erythromycin base and lactobiono- δ -lactone; erythromycin stearate, which includes both the stearic acid salt of erythromycin and the stearic acid ester of erythromycin; and erythromycin ethyl succinate, which is the ester of erythromycin and ethyl succinic acid.

The "penetrating carrier" is more fully described hereinafter.

By "penetration-enhancing amount" of the penetrating carriers described herein is meant an amount sufficient to deliver clinically effective amounts of erythromycin or a derivative of erythromycin through intact skin within 18 hours. Penetration enhancing amounts of the penetration enhancer disclosed herein can be determined by the skin penetration testing techniques described hereinafter.

By "skin disorders and dermatoses of bacterial origin" is meant both primary infectious (pyogenic) processes, and secondary cutaneous manifestations of infection elsewhere in the body. Among the primary pyodermas are included impetigo, such as impetigo contagiosa and impetigo bullosa; deep and superficial folliculitis, including follicular impetigo, sycosis barbae, pyoderma faciale and folliculitis decalvans; furuncles and carbuncles; paronychia infections; ecthyma; erysipelas; cellulitis; lymphangitis; and erythrasma. Typical secondary bacterial infections include those caused by burns, eczematous dermatitis, including exfoliative erythrodermas; chronic ulcers; dermatophytosis; traumatic lesions; and vesicular or bullous eruptions such as varicella and pemphigus. Other distinctive clinical dermatologic entities include secondary folliculitis such as acne conglobata or hidradenitis suppurativa; infectious eczematoid dermatitis; intertrigo; pilonidal and sebaceous cysts; infectious gangrene; and necrotizing ulcers. Unusual cutaneous infections include cutaneous diphtheria; listeriosis; bartonellosis; and animal-borne diseases.

A more detailed description of the diagnosis and antibiotic therapy of the foregoing and related diseases can be found in *Dermatology in General Medicine*, Fitzpatrick, et.al., eds., pages 1679 et seq. (1971).

"Diisopropyl sebacate" is the 2-propyl diester of decanedioic acid. It is slightly soluble in water, and freely soluble in alcohols, esters and ketones.

Diisopropyl sebacate is a known compound; it is an article of commerce, available commercially from a variety of sources in laboratory and/or industrial quantities.

By "comprising" is meant that various other compatible ingredients may be present in the compositions in such a proportion as will not adversely affect the stability and penetrating effectiveness of the basic composition. The term "comprising" thus encompasses and includes the more restrictive terms "consisting" and "consisting essentially of" within its scope.

All percentages are by weight, unless otherwise specified herein.

The compositions of the present invention comprise (1) a minor proportion of an antibiotic agent selected from erythromycin and derivatives of erythromycin; and (2) a major proportion of pharmaceutically-acceptable penetrating carrier, comprising: (a) a penetration-enhancing amount of diisopropyl sebacate; and (b) the balance comprising a dermatologically acceptable alcohol.

In general, the penetration enhancer is effective in concentrations of from about 20% to about 80%, and above. Preferably, the compositions will contain sufficient penetration enhancer to promote penetration of the erythromycin, and sufficient dermatologically acceptable alcohol to provide a conveniently usable and esthetically acceptable liquid, lotion, gel, or the like. Thus, the compositions of the present invention preferably contain from about 30% to about 60% of the penetration enhancer, most preferably about 30%, and from about 40% to about 70% of the alcohol.

Of course, optional ingredients may be added, including pigments and perfumes to provide cosmetic acceptability, emollients, humectants, and natural oils to provide skin conditioning benefits, and thickening, gelling, and film forming agents such as carboxymethyl cellulose, polyethylene glycols,

carbomers, and "Carbosets". Preservatives, such as the "parabens" (methyl, ethyl, propyl and butyl esters of parahydroxybenzoic acid), and benzyl alcohol can be used to provide protection against contamination by fungi and non-susceptible bacteria.

The foregoing compositions preferably comprise from 0.1% to 10% of the antibiotic agent, more preferably from 2% to 5% erythromycin. Most preferable, from the standpoint of efficacy, stability, and safety, is a concentration of erythromycin or erythromycin derivative which provides about 4% erythromycin base equivalent.

Preferred antibiotic agents are erythromycin base and organic ester derivatives of erythromycin, especially erythromycin ethyl succinate. Also preferred are erythromycin derivatives selected from the group consisting of erythromycin propionate, erythromycin estolate, and erythromycin stearate. Selection of an antibiotic agent from among erythromycin and derivatives of erythromycin will depend in many cases on the solubility of erythromycin or the erythromycin derivative in the particular penetrating vehicle being used. In some cases, limited solubility of the antibiotic agent in the vehicle selected will determine the maximum concentration of antibiotic that can be used.

An especially preferred composition comprises (1) about 4% erythromycin; (2) about 30 diisopropyl sebacate; and (3) about 66% ethanol.

Dermatologically acceptable alcohols can be selected from the simple short-chain alcohols and the toxicologically safe polyols. Examples include ethanol, isopropanol propylene glycol, and glycerol. Especially preferred is a member selected from the group consisting of ethanol, isopropanol, and mixtures thereof. While the examples herein employ absolute ethanol, it is to be understood that both absolute (100%) and 95% ethanol are acceptable for the practice of this invention. Denatured ethanol can be used so long as the denaturant is toxicologically acceptable and does not affect the stability of the antibiotic or its efficacy, or the penetrating characteristics of the vehicle.

Water can be present in the compositions of this invention without deleteriously affecting the penetration of the antibiotic agent. However, the presence of substantial amounts of water causes erythromycin and erythromycin derivatives to become unstable on prolonged storage. Thus, the preferred compositions of this invention are substantially water-free or contain less than about 5% water. In light of this, the preferred compositions which contain ethanol as a dermatologically acceptable alcohol will employ absolute ethanol.

When the compositions of the present invention are used in the treatment of skin disorders and dermatoses of bacterial origin, the amount of composition topically applied and treatment regimen will vary, depending upon the particular disease being treated and the susceptibility of the causative organisms to erythromycin antibiotics, the patient, the severity of the disease state, and like factors which must be considered by the attending physician.

When the compositions of this invention are used in the topical treatment of acne, the preferred treatment will comprise applying a safe and effective amount of the composition to the afflicted situs on the skin. An effective dosage is about 0.1 mg/cm² to about 25 mg/cm² of the antibiotic composition per day. It is preferred to cleanse the skin prior to treatment, and any soap or detergent composition suitable for washing the skin can be employed. The treatment is more effective if topical applications are made 2 to 4 times per day.

The problems encountered in the topical administration of antibiotics have been the stability of the drug in the carrier or vehicle and the development of a carrier vehicle allows the drug to penetrate the skin, thus facilitating the delivery of the antibiotic. The selection of the appropriate carrier for an antibiotic agent is critical. Not all delivery systems and penetrating aids will facilitate the diffusion of a given antibiotic agent through the skin barrier. The penetrating carrier must be compatible with the antibiotic; it must be not toxic; and the formulation must be stable.

Skin penetration testing

In order to determine the best penetrating carriers for erythromycin and derivatives of erythromycin, a diffusion study was carried out using the skin of hairless mice. Briefly, the study employed mouse skin which was placed in a vertical position between a lower, capped, diffusion cell and an upper, open cell. A normal saline solution was added to the lower diffusion cell, abutting the subcutaneous side of the mouse skin, and the test composition comprising a solution of the antibiotic agent and the penetrating carrier was added to the diffusion cell abutting the epidermal side of the mouse skin. A small glass bead was added to the lower diffusion cell to provide mixing.

This cell assembly was kept in a constant-temperature room at about 31°C. The diffusion time used for the test was about 18 hours.

At the end of this time period, each diffusion cell assembly was opened and the diffusate from the cell abutting the subcutaneous side of the skin was filtered by expressing the liquid through a disposal filter attached to a plastic disposable syringe. This diffusate was then submitted for microbiological agar diffusion assay done in accordance with the procedure described at 21 C.F.R. 436.105. This test provides a measure of the passage of active erythromycin antibiotic through the skin.

Table 1 lists the penetrating carrier and other tested materials and their activity, as micrograms erythromycin which penetrated through the mouse skin, per milliliter (μg/ml) of diffusate.

TABLE 1

	Test material	Hrs.	Penetration- μg/ml.
5	Propylene glycol dipelargonate	18	248
	Polyoxypropylene 15 stearyl ether	18	95*
	Standamul HE™(Polyol fatty acid ester)	18	0*
	Propylene glycol	18	0*
	Benzyl alcohol	18	0*
10	Carbowax™ 400	18	0*
	Octyl alcohol	18	132*
	1,2-Butanediol	18	0*
	2,3-Butanediol	18	0*
	1,3-Butanediol	18	0*
15	POE ester of oleyl alcohol	18	121*
	Phenethyl alcohol	18	0*
	Oleyl alcohol	18	197
	Cyclohexanol	18	0*
	2-Phenoxyethanol	18	0*
20	Lauryl alcohol	18	254
	Dioctyl adipate	18	234
	Diethyl adipate	18	0*
	Dicapryl adipate	18	235
	Diisopropyl adipate	18	103*
25	Diisopropyl sebacate	18	268
	Dibutyl sebacate	18	207
	Diethyl sebacate	18	158
	Dimethyl sebacate	18	91*
	Dioctyl sebacate	18	181
30	Dibenzyl sebacate	18	132*
	Diethyl suberate	18	0*
	Dibutyl suberate	18	36*
	Dioctyl azelate	18	180
	Dibutyl azelate	18	86*
35	Dimethyl azelate	18	64*
	Dibutyl succinate	18	73*
	Diethyl succinate	18	0*
	Dibutyl phthalate	18	227
	Dimethyl phthalate	18	0*
40	Didecyl phthalate	18	55*
	Ethyl myristate	18	296
	Butyl myristate	18	243
	Isopropyl palmitate	18	285
	Ethyl laurate	18	243
45	Decyl oleate	18	126*
	2-ethyl-hexyl pelargonate	18	228
	Isopropyl isostearate	18	204
	Butyllaurate	18	214
	Benzyl benzoate	18	230
50	Butyl benzoate	7	177
	Ethyl benzoate	18	0*
	Benzyl 2-acetoxy benzoate	18	0*
	Hexyl laurate	18	201
	Ethyl caprate	18	236
55	Ethyl caprylate	18	162
	Ethyl caproate	18	66*
	Butyl stearate	18	198
	Benzyl salicylate	18	236
	Ethyl salicylate	18	131*
60	20% Benzyl benzoate+20% ethyl laurate	18	253
	10% Benzyl salicylate+40% Ethyl laurate	18	269
	40% Dibutyl sebacate+10% Benzyl salicylate	18	241

* Does not represent acceptable delivery

65 0* indicates that no readable zone was produced at the dilution tested.

In addition, the following materials were tested in the foregoing manner and were not found to deliver clinically effective concentrations of erythromycin.

5	Squalane
	Castor oil
	N-methyl-2-pyrrolidone
	Ethyl lactate
	2,4-pentanedione
	Silicone 344
10	Cyclohexanone
	Salicylic acid+isopropyl myristate
	Salicylic acid+propylene glycol
	Salicylic acid+dibutyl sebacate
	Salicylic acid+propylene glycol dipelargonate
15	Solketal™+Propylene glycol dipelargonate
	Propylene glycol dipelargonate+lactic acid
	Propylene glycol dipelargonate+ethyl lactate
	Dimethyl sulfoxide
20	Propylene glycol+monoolein

The following Example illustrates the practice of this invention, without intending to be limiting thereof.

	Example	
	Ingredient	Weight %
25	Erythromycin base	4%
	Ethanol	66%
	Diisopropyl sebacate	30%

The above ingredients are blended mechanically to provide a fluid composition suitable for topical application to skin. In the composition of Example 1, the diisopropyl sebacate markedly enhances the skin penetration of the erythromycin.

The composition of Example 1 is especially useful in the treatment of common acne (*acne vulgaris*) and similar acneiform bacterial dermatological conditions.

A person afflicted with acne lesions is treated by topically applying the composition of Example 1 to the afflicted areas of skin (typically the face, neck and shoulders) at a rate of 3 mg./cm² of antibiotic composition twice a day for 6 weeks. At the end of this period, there is a substantial reduction in the number of acne lesions, and the inflammation is reduced.

Erythromycin ethylsuccinate can be substituted for the erythromycin base, in an amount which provides 4% erythromycin base equivalent, with equivalent results.

Claims

1. A composition for topical application to skin in the treatment of skin disorders and dermatoses of bacterial origin, characterized in that it comprises:

(1) a minor proportion of an antibiotic agent selected from erythromycin and derivatives of erythromycin; and

(2) a pharmaceutically-acceptable penetrating carrier comprising

(a) a penetration enhancing amount of diisopropyl sebacate; and

(b) the balance comprising a dermatologically acceptable alcohol, or mixture thereof.

2. A composition according to Claim 1 characterized in that the dermatologically acceptable alcohol is selected from ethanol, isopropanol, and mixtures thereof.

3. A composition according to Claim 1 characterized in that it comprises from 0.1% to 10% by weight of the antibiotic agent.

4. A composition according to Claim 2 characterized in that the antibiotic agent is erythromycin.

5. A composition according to Claim 3 characterized in that it comprises from 2% to 5% by weight of erythromycin.

6. A composition according to Claim 2 characterized in that the antibiotic agent is an organic ester derivative of erythromycin.

7. A composition according to Claim 6 characterized in that the derivative of erythromycin is selected from erythromycin propionate, erythromycin estolate, erythromycin stearate, erythromycin ethyl succinate, erythromycin glucoheptonate, and erythromycin lactobionate.

8. A composition according to Claim 5 characterized in that it comprises

(1) about 4% by weight of erythromycin;

(2) about 30% by weight of diisopropyl sebacate; and

(3) about 66% by weight of ethanol.

Patentansprüche

1. Zusammensetzung zur topischen Anwendung auf die Haut bei der Behandlung von Hautstörungen und Dermatosen bakteriellen Ursprungs, dadurch gekennzeichnet, daß es
5 (1) einen geringen Anteil an einem antibiotischen Mittel ausgewählt aus Erythromycin und Derivaten von Erythromycin; und
(2) einen pharmazeutisch verträglichen, eindringenden Träger, enthaltend
(a) eine das Eindringen verbessernde Menge an Diisopropylsebacat und
(b) den Rest, der einen dermatologisch verträglichen Alkohol oder Gemische davon umfaßt,
10 enthält.
2. Zusammensetzung gemäß Anspruch 1, dadurch gekennzeichnet, daß der dermatologisch verträgliche Alkohol ausgewählt ist aus Ethanol, Isopropanol und Gemischen daraus.
3. Zusammensetzung gemäß Anspruch 1, dadurch gekennzeichnet, daß sie 0,1 % bis 10 Gew.-% des antibiotischen Mittels enthält.
15 4. Zusammensetzung gemäß Anspruch 2, dadurch gekennzeichnet, daß das antibiotische Mittel Erythromycin ist.
5. Zusammensetzung gemäß Anspruch 3, dadurch gekennzeichnet, daß sie 2 % bis 5 Gew.-% Erythromycin enthält.
6. Zusammensetzung gemäß Anspruch 2, dadurch gekennzeichnet, daß das antibiotische Mittel
20 ein organisches Esterderivat von Erythromycin ist.
7. Zusammensetzung gemäß Anspruch 6, dadurch gekennzeichnet, daß das Erythromycinderivat ausgewählt ist aus Erythromycinpropionat, Erythromycinestolat, Erythromycinstearat, Erythromycinethylsuccinat, Erythromyninglucoheptonat und Erythromycinlactobionat.
8. Zusammensetzung gemäß Anspruch 5, dadurch gekennzeichnet, daß sie
25 (1) etwa 4 Gew.-% Erythromycin;
(2) etwa 30 Gew.-% Diisopropylsebacat und
(3) etwa 66 Gew.-% Ethanol
enthält.

30 Revendications

1. Composition pour application topique sur la peau dans le traitement des maladies de peau et dermatoses d'origine bactérienne, caractérisée en ce qu'elle renferme:
(1) une proportion mineure d'un antibiotique choisi parmi l'érythromycine et ses dérivés; et
35 (2) un véhicule pénétrant, pharmaceutiquement acceptable comprenant
(a) une quantité de sébacate de diisopropyle favorisant la pénétration; et
(b) un alcool dermatologiquement acceptable ou un mélange de cet alcool, pour le complément à 100 %.
2. Composition selon la revendication 1, caractérisée en ce que l'alcool dermatologiquement
40 acceptable est choisi parmi l'éthanol, l'isopropanol et leurs mélanges.
3. Composition selon la revendication 1, caractérisée en ce qu'elle comprend de 0,1 à 10 % en poids de l'antibiotique.
4. Composition selon la revendication 2, caractérisée en ce que l'antibiotique est l'érythromycine.
5. Composition selon la revendication 3, caractérisée en ce qu'elle comprend de 2 à 5 % en poids
45 d'érythromycine.
6. Composition selon la revendication 2, caractérisée en ce que l'antibiotique est un ester organique de l'érythromycine.
7. Composition selon la revendication 6, caractérisée en ce que le dérivé d'érythromycine est choisi parmi le propionate d'érythromycine, l'estolate d'érythromycine, le stéarate d'érythromycine,
50 l'éthyl succinate d'érythromycine, le glucoheptonate d'érythromycine et le lactobionate d'érythromycine.
8. Composition selon la revendication 5, caractérisée en ce qu'elle renferme:
(1) environ 4 % en poids d'érythromycine,
(2) environ 30 % en poids de sébacate de diisopropyle, et
55 (3) environ 66 % en poids d'éthanol.

60

65